Case report

Hepatocellular carcinoma in a patient with focal nodular hyperplasia

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Background

Focal nodular hyperplasia is an uncommon liver tumour that typically requires no therapeutic intervention.

Case outline

A 43-year-old woman with a 20-year history of oral contraceptive use presented with symptomatic bilateral liver masses. Biopsy revealed hepatocellular carcinoma in the right hemiliver and focal nodular hyperplasia in the left hemiliver. At operation, the patient was noted to have multiple liver nodules bilaterally, and all intraoperative biopsies were consistent with focal nodular hyperplasia including a biopsy taken from the region that demonstrated carcinoma preoperatively. Because of the earlier biopsy results and the patient's preoperative symptoms, a right hemihepatectomy was performed. Final pathology revealed hepatocellular carcinoma directly adjacent to an area of focal nodular hyperplasia, as well as multiple other areas of hyperplastic liver tumour.

Discussion

Although focal nodular hyperplasia is believed to be benign, few studies have followed patients with this tumour beyond three years. Longer-term follow-up studies are needed to determine the natural history of focal nodular hyperplasia, potentially focussing on a subset of patients with either diffuse tumours or prolonged oral contraceptive use.

Keywords

Focal nodular hyperplasia, hepatocellular carcinoma, liver tumour.

Introduction

Focal nodular hyperplasia (FNH) is a rare hepatic tumour comprising hyperplastic liver parenchyma, predominantly affecting women of late reproductive age [1–6]. While lesions have been found simultaneously in rare cases of fibrolamellar carcinoma and in a single case of hepatocellular carcinoma, FNH is generally considered a benign tumour with no malignant potential. We report the case of a 43-year-old woman with diffuse FNH and a hepatoma directly contiguous to an area of FNH.

Case Report

A 43-year-old woman presented with recent right upper quadrant pain and right shoulder pain. Initial work-up included an ultrasound scan, which demonstrated a mass lesion in the liver, and a CT scan, which revealed a large lesion in the right lobe of her liver as well as a smaller mass in the left lobe. The remainder of the liver appeared inhomogeneous with intact vasculature.

The patient had hepatitis A as a child. In addition, she had been on oral contraceptives for 20 years. She took no medicines. Physical examination was entirely within normal limits. Laboratory rests showed elevations in plasma levels of alkaline phosphatase to 161 IU/L and aspartate aminotransferase to 146 IU/L. Her haematocrit was mildly decreased at 34.7%. Coagulation studies, platelets, white blood cell count, electrolytes, bilirubin, and albumin were all within normal limits. Alpha fetoprotein was mildly elevated at 13 ng/ml. CT-guided needle biopsy revealed hepatocellular carcinoma in the mass in her right lobe and FNH in the left lobe mass.

At abdominal exploration, the patient was noted to have multiple liver nodules bilaterally with a gross appearance characteristic of FNH. Frozen section biopsies were taken from the dominant lesion in each lobe (consistent

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with the two masses noted on CT scan) as well as from the falciform ligament. All were reported to contain FNH without histological evidence of malignancy. In view of the patient's history of pain secondary to the tumour in the right lobe of liver as well as the preoperative tissue diagnosis, a right hemihepatectomy was performed. The patient had an unremarkable hospital course and was discharged to home on the eighth postoperative day.

Gross pathology revealed an 18 × 15 × 9 cm sized right hemiliver. The most striking feature was a 7 × 6.5 × 3.5 cm area composed of a collection of light tan nodules. These smaller nodules ranged from 0.3 to 3 cm in maximal dimension. Focal areas of haemorrhagic necrosis were noted in the centre of this area. Separate from this dominant area there were widely scattered, multiple nodules up to 1.5 cm in size, located in otherwise normal liver parenchyma.

Microscopically, the area of nodular aggregates showed moderately differentiated hepatocellular carcinoma. Focally, there was marked cytologic atypia with bizarre, enlarged nuclei, as well as multiple atypical mitotic figures. An area of parenchyma immediately adjacent to the hepatocellular carcinoma nodules demonstrated bile duct proliferation and moderate chronic inflammation (Figure 1). Surgical margins were free from tumour.

Multiple other nodules showed hyperplastic tissue with bile duct proliferation similar to that found adjacent to the tumour described above. These lesions were consistent with FNH. The liver parenchyma surrounding these areas of FNH was normal. A single lymph node and the gallbladder were also free from tumour. The final stage of the tumour was T3N0M0, with multiple foci of FNH in otherwise uninvolved liver.

A routine MRI scan obtained three months postoperatively to follow disease progression demonstrated a new 6 cm mass in the medial segment of the left lobe of liver. CT-guided biopsy revealed recurrent hepatocellular carcinoma. As part of an evaluation to determine the patient's candidacy for possible liver transplantation, a chest CT revealed an indeterminate 5 mm nodule in the right lower lobe (superior segment). Thoracoscopic biopsy of this lesion revealed metastatic hepatocellular carcinoma. The patient subsequently underwent chemoembolisation of her liver six months postoperatively. Some decrease was noted in the degree of liver disease; however, she rapidly developed multiple new pulmonary metastases. The patient was then offered systemic chemotherapy as part of a clinical trial with doxil and gemcitabine but has subsequently been lost to follow-up.

Discussion

FNH is a well-circumscribed liver tumour typically grossly comprising of a central fibrous scar surrounded by hyperplastic nodules [3,4,7,8]. Histologically, the arterial and venous channels in the fibrous body are accompanied by proliferating bile ducts [9,10]. The pathogenesis of FNH continues to be controversial, with various authors considering the entity to be a neoplasm, a hamartoma, or a response to either ischaemia, focal injury, or to a congenital abnormality of portal tracts [2–4,10–12]. No clear aetiology in the development of FNH has been identified. Oral contraceptive use has been implicated, but this remains controversial [13–17].

Initially classified in 1958, more than 80% of FNH

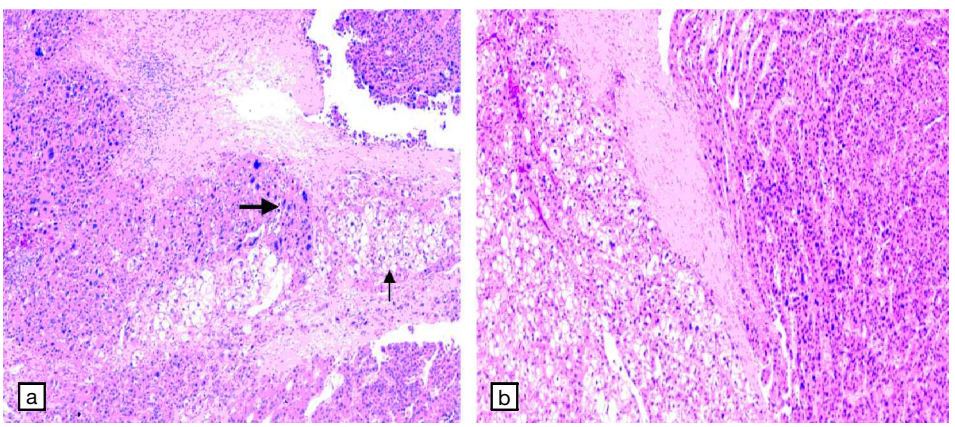

Figure 1. *(a) Haematoxylin and eosin (H&E)-stained section shows hepatocellular carcinoma (large arrow) directly adjacent to areas of FNH (small arrow). (b) Higher power section showing FNH on the left and hepatocellular carcinoma on the right.*

lesions are solitary and less than 5 cm in diameter [3,7,9]. Most lesions exhibit no growth over time, and haemorrhage into nodules is exceedingly rare [7,18]. Since FNH is typically asymptomatic, little information on its long-term natural history is available. A recent study by Mathieu et al., following 136 women with FNH via serial MRIs for an average follow-up of 25 months, showed change in tumour size in only four patients [17]. Another series of 53 patients with FNH, monitored with multimodality radiological studies, showed no evidence of malignancy in a mean follow-up of 32 months, with an increase in tumour size in five patients and a decrease in tumour size in two patients [19]. These results contrast with an earlier report in which 16 patients with FNH were followed with ultrasound for a mean follow-up of 33 months. Tumour size was unchanged in only half the patients, tumour size was reduced in seven patients, and tumour disappearance was noted in one patient [20]. The alterations in tumour size in all studies were independent of oral contraceptive use.

While simultaneous occurrence of FNH with fibrolamellar carcinoma has been rarely described [21–23], FNH is believed to have no potential for malignant degeneration. The sole previous report of hepatocellular carcinoma and FNH co-existing in a patient demonstrated that the tumours had separate clonal origin [24]. The combination of a presumed benign natural history without fear of dedifferentiation has led to expectant management being the mainstay of FNH therapy. Surgery is reserved for symptomatic patients, although some sources advocate operating for lesions that enlarge due to oral contraceptives [1,6,19,25–29]. In addition, despite multimodality imaging techniques including ultrasound, dynamic CT, SPECT, MRI, ^{99}T-sulphur colloid scan, cholescintigraphy, and positron emission tomography, FNH may be difficult to differentiate from hepatic adenoma or adenocarcinoma preoperatively [6,17,28,30–34].

This case demonstrates the first reported example of hepatocellular carcinoma arising in a liver with diffuse FNH. Notably, an area of FNH was found directly adjacent to the cancer on pathological examination. Although the two lesions were directly contiguous, there is no evidence that the cancer arose directly from the area of FNH. Without the benefit of following this lesion radiographically or histologically over time, there is no way of knowing if a FNH lesion underwent malignant degeneration. Nonetheless, it is intriguing that the cancerous tumour was surrounded by areas of FNH. This intimate association is underscored by the intraoperative frozen section biopsy of the tumour site. Although performed under direct vision, Tru-cut® biopsy still showed only FNH in the area where a hepatoma was eventually diagnosed on final pathology.

The findings seen in this patient demonstrate the importance of gaining a more complete understanding of the natural history of FNH. To date, only a few studies following patients with FNH for two to three years have been performed [17,20,35]. Perhaps certain subsets of patients with FNH have an incidence of malignant degeneration. Certainly, the patient described had a more severe and diffuse case of FNH than is typically described, which might lead to a more aggressive phenotype over time. In addition, she had a 20-year history of oral contraceptive use. While the relationship between contraception and FNH is far from clear [13–17], prolonged usage may represent a risk factor for growth or eventual malignant transformation.

Based on the available data, conservative therapy for patients with FNH continues to be appropriate. Although operative excision may be performed safely with minimal morbidity, symptomatic FNH continues to be the only clear indication for this procedure. Nonetheless, this patient poses a possible challenge to the idea that all FNH lesions — regardless of size and prolonged oral contraceptive use — are benign lesions. Further multimodal study of the natural history of this disease is thus warranted to assess the malignant potential of FNH and possible alterations to accepted treatment protocols.

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